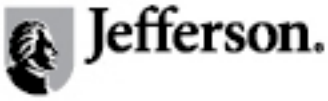

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A glance at imaging bladder cancer.

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A glance at imaging bladder cancer

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Abstract

Purpose—Early and accurate diagnosis of Bladder cancer (BCa) will contribute extensively to the management of the disease. The purpose of this review was to briefly describe the conventional imaging methods and other novel imaging modalities used for early detection of BCa and outline their pros and cons.

Methods—Literature search was performed on Pubmed, PMC, and Google scholar for the period of January 2014 to February 2018 and using such words as “bladder cancer, bladder tumor, bladder cancer detection, diagnosis and imaging”.

Results—A total of 81 published papers were retrieved and are included in the review. For patients with hematuria and suspected of BCa, cystoscopy and CT are most commonly recommended. Ultrasonography, MRI, PET/CT using ^{18}F-FDG or ^{11}C-choline and recently PET/MRI using ^{18}F-FDG also play a prominent role in detection of BCa.

Conclusion—For initial diagnosis of BCa, cystoscopy is generally performed. However, cystoscopy can not accurately detect carcinoma insitu (CIS) and can not distinguish benign masses from malignant lesions. CT is used in two modes, CT and computed tomographic urography (CTU), both for dignosis and staging of BCa. However, they cannot differentiate T1 and T2 BCa. MRI is performed to diagnose invasive BCa and can differentiate muscle invasive bladder carcinoma (MIBC) from non-muscle invasive bladder carcinoma (NMIBC). However, CT and MRI have low sensitivity for nodal staging. For nodal staging PET/CT is preferred. PET/MRI

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provides better differentiation of normal and pathologic structures as compared with PET/CT. Nonetheless none of the approaches can address all issues related for the management of BCa. Novel imaging methods that target specific biomarkers, image BCa early and accurately, and stage the disease are warranted.

Keywords

Bladder Cancer; Imaging; Cancer Diagnosis; CT; MRI; PET/CT

Introduction

Bladder cancer (BCa) presents as the second most common genitourinary malignancy [1–3]. Early and accurate diagnosis can reduce mortality [4]. A typical symptom of BCa is painless hematuria [5]. For initial diagnosis, urine analyses are commonly performed. Imaging plays an important role in assessing the extent of BCa for which computed tomography (CT), ultrasonography (US), magnetic resonance imaging (MRI) and molecular imaging modalities such as positron emission tomography/computed tomography (PET/CT), or positron emission tomography/magnetic resonance imaging (PET/MRI) are used [6, 7]. The purpose of this review was to briefly describe the conventional imaging methods, and new imaging modalities used for imaging BCa and outline their pros and cons. In so doing, a literature search for the past four years (January 2014 to February 2018) was performed on Pubmed, PMC, and Google scholar, using such words as “bladder cancer and bladder tumor detection, diagnosis and imaging”. A total of 81 published papers were found and are included in this review. The approaches described herein to image suspicious BCa are given in Table 1 and are summarized below.

Cystoscopy

Cystoscopy is performed in seven following different ways.

a) White Light Cystoscopy—White light cystoscopy (WLC), a widely available technique, that allows visualization of the mucosa within the bladder, is considered a gold standard method for detecting BCa [8]. There are two forms of WLC, rigid and flexible cystoscopy (FC). Rigid cystoscopy provides better image quality, enables working with a large lumen, and provides improved flow. FC on the other hand allows alternative patient positioning, easy passage, and enables examination of all parts of the bladder [8]. Therefore, FC is usually applied for initial assessment of patients. However, FC may miss up to 10% of papillary tumors. Furthermore its small working channel lumen does not allow resection of BCa [9]. Although technology has improved the WLC image quality significantly, WLC cannot reliably determine flat and carcinoma in situ (CIS) lesions, and cannot distinguish benign lesions from malignant masses. Such a distingtion is particularly important when Transurethral Resection of Bladder (TURB) is to be performed [9–11]. However, cystoscopy is recommended by national comprehensive cancer network (NCNN) and American urological association (AUA) guidelines for imaging patients with macroscopic hematuria [5, 12].

Other novel endoscopic visualization techniques briefly described below have been developed to overcome some limitations of WLC. Although these methods are helpful for assessment of BCa, they are invasive, time-consuming, and expensive to perform. [9, 13].

b) Computer-Assisted Cystoscopy—For computer-assisted cystoscopy, standard cystoscopy images are assessed with color segmentation system. This system provided 100% accurate detection of cancerous tissue. However false positive (FP) rate is 50% [11]. Therefore, this method is not commonly used.

c) Photodynamic Diagnosis—Photodynamic diagnosis (PDD), in which intravesical photosensitizing agents are introduced into the bladder to accumulate into the tumor cells, provides a helpful evaluation of BCa in the course of TURB. PDD has a higher sensitivity than WLC for detecting CIS and BCa. PDD-guided TURB has a lower recurrence rate than WLC-guided TURB [14]. However, the effect of PDD on progression-free survival is uncertain [9, 13].

d) Narrow Band Imaging—Narrow band imaging (NBI) used for increasing the contrast between the BCa and normal mucosa, enables imaging of mucosal vascular structures [9]. NBI can be helpful to determine whether TURB is required. However, whether its use is associated with a lower recurrence rate remains to be verified [13, 15].

e) Confocal Laser Endomicroscopy—Used for diagnosis and staging of BCa, Confocal Laser Endomicroscopy (CLE) uses fluorescein, administered intravenously or intravesically, and enables high-resolution cellular imaging. CLE is linked with improved surgery results. However, due to limited optical depth penetration, CLE cannot detect disease involving the muscularis propria [9, 16].

f) Optical Coherence Tomography—Optical coherence tomography (OCT) which uses infrared light, distinguishes between the layers of the bladder, and provides imaging of tissue and luminal surfaces with high spatial resolution. Urothelium appears in low intensity, lamina propria in slighgtly high intensity, but with low intensity for muscularis propria. OCT is useful for evaluation of non-muscle invasive BCa non-muscle invasive bladder carcinoma (NMIBC), CIS and recurrent tumor [9].

g) Storz Professional Image Enhancement System—Storz Professional Image Enhancement System (SPIES) employs a camera with four modes to enhance image quality in different clinical situations. The Clara mode enables homogeneous images; the Chroma mode improves the sharpness of the images; and the Spectra A and B modes provide better color contrast. Analysis of outcomes for SPIES-guided TURB remains a work in-progress [13].

Ultrasonography

There are two types of Ultrasonography techniques; a) Two-Dimensional Ultrasonography and b) Contrast Enhanced Ultrasonography.

a) Two-Dimensional Ultrasonography—Two-Dimensional Ultrasonography (2D US) is a widely used and recommended method for evaluating hematuria and for staging, particularly in patients who have allergies to intravenous contrast agents and renal failure (Figure 1) [5, 17–21]. However, according to some publications 2D US is not recommended for the staging of BCa because it may not reveal the true local depth of its invasion [18–21]. Three-dimensional US provides BCa imaging in multiple planes, and may improve the accuracy of staging BCa [19]. A study evaluating the diagnostic accuracy of ultrasound T staging (UTS), in 152 elderly BCa patients, found that UTS results were comparable with those of histological T staging (HTS) [22]. In a 115 patient study, high conformity (75.7%) was found between the UTS and HTS, with 94.5% accuracy for stage T1. In other stages, the accuracy ranged between 84.9% and 91.8%. 2D US is helpful for differentiating the superficial BCa from muscle invasive BCa muscle invasive bladder carcinoma MIBC and can play an important role in planning treatment [22]. A comparative study between US and cystoscopy in 83 patients with low grade BCa, matched with propensity score was calculated from clinicopathological variable factors such as age, gender, tumor multiplicity, size, grade, and intravesical treatment. No significant difference in recurrence rate or in recurrent tumor characteristics was noted [20].

b) Contrast Enhanced Ultrasonography—CEUS is a new technique that uses microbubbles as a ultrasonographic contrast agent to determine the grade and stage of BCa [18]. The use of CEUS was investigated to predict T stage and grade of BCa prior to endoscopic resection in 110 patients suspected of BCa. Results were compared with histology. CEUS had the T stage: Ta sensitivity of 75%; specificity of 95%, T1 sensitivity 65%; specificity 85% and muscle invasion sensitivity 90% with the specificity of 92% [18]. CEUS differentiated high grade (n=110) and low grade (n=82) urothelial BCa with 86% sensitivity, 90% specificity, 88% accuracy, 92% positive predictive value (PPV), and 82% negative predictive value (NPV). For high grade and low grade BCa the sensitivity was 85%, specificity 89%, accuracy 88%, PPV 85%, andNPV was 89% [23]. Similar results were found in another study, in 105 patients (55 low grade and 50 high grade). Time-intensity curve parameters for CEUS showed that the tumor microvessel density can be useful for assessing tumor angiogenesis [24]. Even though, new US methods have been developed, the role of US for staging BCa is not yet clearly defined [19].

Computed Tomography

CT scan is used in two different modes. The first, computed tomographic urography (CTU) can be performed with or without intravenous contrast agent, applied with sufficient phase to exclude a renal tumor and an excretory phase to assess upper urinary tract. CTU provides imaging of urinary system (the kidneys, ureters, bladder, and urethra) and is especially useful for urinary system pathologies. The second mode of CT scan is the conventional CT; this provides examinations of upper-lower abdomen and pelvis. CT is commonly used and is recommended method for staging BCa (Figure 2) [5, 17, 21, 25, 26].

a) Computed Tomographic Urography—In a study of 687 patients, 710 CTU were evaluated to detect BCa. CTU had 91.5% (650/710) accuracy, 86.3% (82/95) sensitivity,

92.4% (568/615) specificity and 63.6% (82/129) PPV. Some false positive results (n=47) were reported due to misinterpretation of images [27].

CTU with enhancement-triggered scan had highest sensitivity and NPV in corticomedullary phase (CMP). Therefore, CMP is recommended for bladder evaluation in patients with gross hematuria [28, 29]. CTU with enhancement-triggered scan and FC were compared in 435 patients to detect BCa. Both methods detected BCa in 48 patients. CTU had 87% sensitivity, 99% specificity, 91% PPV, and 98% NPV, while FC had 87% sensitivity, 10% specificity, 98% PPV, and 98% NPV [30].

Diagnostic performance of CTU was compared with cystoscopy in 177 patients. CTU performed better with 96.3% sensitivity, 86.4% specificity, 92.8% diagnostic accuracy, 92.9% PPV, and 92.7% NPV. The arterial acquisition phase diagnosed the lesions with the highest accuracy, and demonstrated 93.4% of all lesions [31].

b) Computed Tomography—CT of 231 BCa patients, following radical cystectomy (RC) and pelvic lymphadenectomy, had 93.6% specificity and 52.6% sensitivity. For local staging, the accuracy was 78%. Overstaging was low (6%) [32].

In a study of 206 patients with invasive BCa, increased bladder wall thickness, lymph node (LN) > 5mm in size, and associated with high risk of death, were imaged by CT. Results were helpful for prognostic information and MIBC management [25].

CT is faster and more cost-effective than MRI, but it is associated with the risk of ionizing radiation, high interobserver variability, and can neither differentiate bladder wall muscle layers, nor can it reliably distinguish T1 from T2 disease. Furthermore, its specificity and sensitivity are low for extravesical extension of early stage BCa and small metastatic lesions of BCa.[17, 21, 25, 26, 32–34].

Dual energy spectral CT is a relatively new method that provides multiparameteric imaging of the urinary system. On the monochromatic images, a threshold value of 73.4 Hounsfield unit demonstrated high sensitivity (77.0%) and specificity (82.5%) for differentiating posterior wall BCa from benign prostate hypertrophy [35].

Magnetic Resonance Imaging

MRI is used for preoperative staging and nodal imaging (Figure 3) of BCa for management of T2 or more advanced disease. MR Urography (MRU) which can be performed without use of contrast agent, is a suitable method for imaging patients with renal failure or those with allergies for iodinated contrast agent. Advanced MRI protocols described below provide functional information and can improve the efficacy for imaging BCa [5, 34, 36].

a) Morphologic MRI—MRI, unlike CT does not use ionizing radiation, offers superior soft tissue contrast, and provides more anatomical and functional information [19]. MRI also differentiates MIBC from NMIBC, and visualizes extramural invasion, T3b and T4 disease [36].

Bladder distension level during MRI affects interpretation of the images [34]. T1-weighted (T1W)-MRI visualizes perivesical fat tissue infiltration, pelvic lymphadenopathy and bone metastasis. The detrusor muscle and BCa present similar signal intensity, and compromises the differentiation of bladder wall invasion on T1W-MRI without contrast. T2-weighted (T2W) MRI is superior to T1W-MRI for differentiation of NMIBC from MIBC. Furthermore, T2W-MRI can distinguish urine from the intraluminal BCa [19, 34]. 3Tesla (3T) MRI is better than 1.5Tesla (1.5T) MRI with regard to resolution, differentiation of tumor from normal tissues, and determination of the depth of tumor invasion [33]. MRI however cannot provide detailed tissue characterization and can overestimate the degree of bladder wall invasion after TURB or chemo-radiotherapy [34].

Split-bolus CTU, MR urography (MRU), and FC were compared in 150 patients for diagnosis of BCa which were verified with histopathology. CTU detected tumors with 61.5% sensitivity, 94.9% specificity, 53.3% PPV, and 96.3% NPV, while MRU detected tumors with 79.9% sensitivity and 93.4% specificity, 52.6% PPV and NPV 97.1%. The number of bladder lesions detected using FC were 32, MRU 19, and CTU 15. Split-bolus CTU or MRU cannot replace cystoscopy in patients with hematuria [37].

A review of 24 publications for diagnostic performance for local staging of MIBC with pathologic confirmation showed that 3T-MRI had higher specificity (93%) than those using 1.5T-MRI (83%). Studies using multiparametric MRI (conventional+≥2 functional sequences) showed the highest accuracy with sensitivity of 94% and specificity of 95% [38].

b) Diffusion-weighted (DW) MRI—DW-MRI is driven by the Brownian motion of water molecules that changes the apparent diffusion coefficient (ADC) value between normal tissue and tumor [19, 34, 39, 40]. The ADC value correlates with cell cycle and proliferative biomarkers [41, 42].

DW-MRI and Dynamic contrast-enhanced (DCE)-MRI at 3T were investigated for aggressiveness of BCa in 59 patients. The combination of ADC and wash-out rate determined the BCa aggressiveness with 96.7% sensitivity, 94.9% specificity, and 95.7% accuracy [43]. Also, ADC was useful for determining the recurrence and progression risk of BCa [19, 40, 44–46]. DWI-MRI however, helps distinguish benign and malignant bladder lesions, for staging, and for the assessment of efficacy of chemo-radiotherapy treatment [36]. DW-MRI does not require contrast agent, therefore DW-MRI can be used in patients with renal failure or allergies to contrast agents [39].

Qualitative and quantitative imaging characteristics of MRI and DWI-MRI were compared for detecting pelvic LNs in 36 BCa patients prior to cystectomy. Results were correlated with histopathology. The short axis (>5mm) LN imaging had 88% sensitivity and 75% specificity, the long axis (>6mm) LN imaging had 88% sensitivity and 71% specificity. ADC (< 1.35 mm and normalized to muscle) had 75% sensitivity and 68% specificity, and, in the absence of fatty hilum, the sensitivity and specificity were 75% and 71% respectively [40].

Normalized ADC (nADC) of tumor, which was calculated by ADC(tumor)/ADC (reference tissue) using urine in the bladder and from muscles as a reference, was superior to ADC for estimating grade of BCa [47].

The accuracy of differentiating muscle invasion and perivesical fat invasion were found higher with DW-MRI and MRI combined, than MRI alone, for T staging in 160 patients [48]. Correlative values between ADC and clinicopathological parameters, such as tumor diameter, grade, and T stage, were also examined. DWI-MRI provided a better tissue contrast than T1-MRI and T2-MRI.

3TDW-MRI was superior to T2W-MRI for deleneating the T stage, for differentiating T1 tumor from T2 or more severe disease, and for showing stalks of BCa [49].

DW-MRI diagnosed BCa with 95% sensitivity and 85% specificity and differentiated MIBC from NMIBC with 85% sensitivity and 90% specificity [50].

For differentiating residual BCa from postoperative changes before a second TURB, in 75 patients, T2W-MRI had 100% sensitivity, only 18% specificity, and 53% accuracy. DCE-MRI had 100% sensitivity, 12% specificity, 50% accuracy and DW-MRI had 92% sensitivity, 82% specificity, 87% accuracy [51].

The use of DW-MRI was investigated for differentiating recurrent tumor from chronic inflammation and fibrosis after surgery. For detecting recurrent tumors the accuracy, sensitivity, specificity, and PPV of DW-MRI were 92.6%, 100%, 81.8%, and 88.9%, respectively which were higher than those of DCE-MRI (59.3%, 81.3%, 27.3%, and 54.2%, respectively). The nADC of recurrent tumors were significantly lower than those of postoperative inflammation or fibrosis [52].

Furthermore, DW-MRI vizualised small LN metastases in normal-sized LNs that conventional imaging modalities would have missed [53]. ADC is a promising parameter for estimation of BCa stage and grade with high sensitivity and specificity [54]. However, DW-MRI has several disadvantages, including low tumor specificity and poor spatial resolution [55].

c) Dynamic contrast-enhanced MRI—Dynamic contrast-enhanced MRI (DCE-MRI), which uses paramagnetic contrast agents, is helpful for depicting tumor vascularity, ischemia-necrosis and mass in the bladder lumen on delayed-phase images. DCE-MRI utilizes T1W sequences providing high-resolution images for detection of BCa. DCE-MRI is helpful for predicting recurrence and chemotherapeutic response [34, 56]. DCE-MRI has strong interobserver agreement and provides high accuracy for distinguishing MIBC from NMIBC [33].

Compared with conventional T2W-MRI alone, the addition of multitransmit 3T-DCE-MRI significantly improved interobserver agreement, and the characterization of BCa especially small malignant tumors and tumors within areas of bladder wall thickening. 3T-DCE-MRI mapping is a promising method to augment BCa imaging beyond the limitations of cystoscopy and CT [33].

The performance of DCE-MRI was evaluated for histological response after chemotherapy on localized urothelial BCa in 12 patients. DCE-MRI was performed prior to chemotherapy to measure the size, thickness, relative enhancement at the arterial and venous phases of each tumor. DCR-MRI helpfully increased selection of patients for localized BCa surgery [57].

d) Lymphotropic Nanoparticle Enhanced MRI—Lymphotropic Nanoparticle Enhanced MRI (LNMRI) uses ultrasmall paramagnetic iron oxide particles. When administered intravenously, they reach LNs through the lymphatics and differentiate benign and malignant LNs. Additional clinical studies are required to determine the role of this method for BCa [58].

e) Multiparametric MRI—Multiparametric MRI (mpMRI) is composed of T1W-MRI, T2W-MRI and functional MRI methods, including DCE-MRI and DW-MRI. mpMRI combines anatomic and functional MRI sequences and plays a role for detection, staging, and local recurrence of BCa [58]. In a recent study, efficacy of mpMRI for staging of BCa after TURB in 45 patients was examined. mpMRI was found both sensitive (92%) and specific (84%) method for MIBC detection. The investigators conluded that, mpMRI may be helpful for local staging of BCa after TURB[59]. However, to assess its efficacy carefully, clinical studies in large patient groups are required.

PET/CT

^{18}F-FDG PET/CT—For nodal metastasis in BCa sensitivity of CT is low. CT may fail to detect nearly 40% of LN metastases [60]. PET/CT is used in oncology for staging, restaging, examining early recurrence, and assessing prognosis. ^{18}Fluorine-2-deoxy-2-fluorodeoxyglucose (^{18}F-FDG), the most commonly used agent in PET/CT imaging, [61] is excreted through the kidneys. Therefore, differentiation of bladder pathology or LN's from physiological ^{18}F-FDG activity is difficult (Figure 4). Forced diuresis may be used to reduce physiological ^{18}F-FDG uptake in the bladder [60, 61].

The sensitivity of ^{18}F-FDG-PET/CT was 56% and the specificity was 98% for nodal metastases as confirmed by histology in 78 patients with BCa scheduled for RC (radical cystectomy). PET/CT was more accurate than CT alone for staging BCa [60].

For initial staging after transurethral biopsy (n=34), PET/CT sensitivity was 87.5%, specificity was 80%, and accuracy was 82%. For CT sensitivity was 66%, specificity 57%, and accuracy was 60%. For restaging BCa (n=43), PET/CT had 85% sensitivity, 60% specificity, and 70% accuracy. CT, for staging, had 80% sensitivity, 50% specificity, and 58% accuracy. The maximum standardized uptake value (SUV_{max}) for primary tumor, ranged from 5.7–30.4 and for LN metastases ranged from 3.5–13.8. Both PET/CT and CT primary tumor detection was 88% and were confirmed by histopathology [62].

^{18}F-FDG-PET/CT and CT with histopathological examination of LNs were compared in 54 locally advanced BCa. PET/CT had 86% specificity, 58 % PPV, and 76% NPV, while CT alone had 89% specificity, 64 % PPV, and 77 % NPV. Both methods had 41% sensitivity for LN metastasis [63].

Role of ^{18}F-FDG-PET/CT as an indicator of response to chemotherapy was investigated in patients with oligometastatic BCa. PET/CT was performed before and after chemotherapy, and results were confirmed with histology. PET/CT predicted histological nodal chemotherapy response in 37 of 43 patients (86%) with LN metastasis following lymphadenectomy. For response, FDG-PET/CT had 100% sensitivity, (37 out of 37), 17% specificity, (1 out of 6), 88% PPV (37 out of 42), and 100% NPV. (1 out of 1) [64].

Preoperative ^{18}F-FDG-PET/CT imaging demonstrated more malignant findings than CT in 47% of high risk MIBC patients. PET/CT also changed the therapy plan for 27% patients [65].

Extravesical ^{18}F-FDG avid lesions, suspicious for malignancy on PET/CT, were correlated with mortality in 211 patients with MIBC. Data suggested that ^{18}F-FDG may be an independent prognostic indicator of mortality [66].

SUV_{max} of early dynamic imaging with ^{18}F-FDG was independent of the SUV_{max} of delayed images. High-grade tumors demonstrated higher SUV_{max} than low-grade tumors in the early dynamic imaging in pT1 tumors. Non-invasive pTa tumors had significantly lower SUV_{max} than higher stage tumors during early dynamic imaging [67].

^{18}F-FDG-PET/CT was compared with CT for LN staging in high-grade T1 tumor [n=9] or MIBC [n=52]. On a patient-based analysis, PET/CT had 47.1% sensitivity, 93.2% specificity, 72.7% PPV, 82.0% NPV, whereas CT had 29.4% sensitivity, 97.7% specificity, 78.2% PPV, 78.2% NPV. PET/CT had low sensitivity for LN staging of MIBC and it did not increase diagnostic accuracy of CT for LN metastasis. This can be affected by various factors, such as patient population, extent of LN dissection, and cut off value of SUV [68].

PET/CT was compared with CT to investigate pelvic LN and distant metastasis in patients with MIBC or high-risk NMIBC. Results were compared with histology. For detecting distant metastasis (n=207), sensitivity of PET and CT was 54%, 41%, respectively. Both scans had similar specificities of 97% and 98%. For pelvic LN involvement (n=93), the CT scan had 46% sensitivity and 98% specificity and PET/CT scan had 68% sensitivity and 95% specificity. Therefore, dual imaging should be performed but only in selected patients [69].

Carbon(C)-11-Choline PET/CT—^{11}C-choline-PET/CT is used for staging of BCa. The main advantage of ^{11}C-choline is its low urinary excretion. Its sensitivity is higher than ^{18}F-FDG for showing local relapse of BCa [70].

For relapse of BCa, ^{11}C-choline-PET/CT had 66.7% sensitivity, 84.6% specificity, 76% accuracy, 80% PPV, and 73.3% NPV. For imaging LNs and distant relapse, this method had 90% sensitivity, 93.3% specificity, 92% accuracy, 90% PPV, and 93.3% NPV. No FP or FN were detected [70].

Tabulating overall survival (OS) and cumulative incidence of cancer-specific death (CSD), the prognostic value of ^{11}C-choline-PET/CT was compared with CT and with histology for preoperative staging in 44 BCa patients. The imaging results were in concordance with OS

and cumulative incidence of CSD. No statistically significant difference was found in OS and CSD between the patient groups for organ-limited versus non-organ-limited disease or LN involvement. ^{11}C-choline PET/CT may play a role to predict prognosis [71].

The role of ^{11}C-choline-PET/CT with Contrast Enhanced Computed Tomography (CECT) was compared for preoperative LN staging in 26 BCa patients and results were confirmed with pathology. On a patient-based analysis, PET/CT had 42% sensitivity and 84% specificity while CECT had 14% sensitivity and 89% specificity. On a region-based analysis, PET/CT had 11% sensitivity and 82% specificity while CECT had 5% sensitivity and 80% specificity. On a lesion-based analysis, PET/CT had 10% sensitivity and 64% specificity and CECT had sensitivity 2% and specificity 63% [72].

^{11}C-choline-PET/CT was compared with histology for preoperative LN evaluation in 59 BCa patients. On a regional-based analysis, PET/CT was positive for primary cancer and/or local relapse in bladder bed in 54.2% of the patients. Pathological LN uptake was found in 23.7% of the patients. For LN metastasis detection, PET/CT had 59% sensitivity, 90% specificity, 71% PPV, 84% NPV and 81% accuracy [73]. A longer lived ^{18}F-choline has not yet been deeply investigated for imaging BCa.

PET/MRI

A relatively recent modality, PET/MRI provides advantages of the high resolution of MRI and metabolic information of PET. PET/MRI differentiates normal and pathologic structures more clearly than PET/CT and facilitates coregistration of the bladder wall, bladder pathologies and pelvic LNs. Therefore PET/MRI is considered to be helpful for the management of BCa [74–76].

Diagnostic performance of MRI and ^{18}F-FDG-PET/MRI using a diuresis protocol was compared in 22 BCa patients. At a score of 3, PET/MRI provided higher accuracy for detection of BCa (86% vs. 77%), pelvic LNs (95% vs. 76%), and nonnodal pelvic malignancy (100% vs. 91%). Additional PET was useful for showing exact level of suspicious nodal/nonnodal findings in the pelvis which were equivocal on MRI alone [74].

A PET/MRI study noted improved bladder wall coregistration and slightly increased detection of bladder masses and pelvic LNs [77].

^{18}F-FDG-PET/MRI was investigated for local or metastatic staging of 11 BCa patients. With T1W and T2W images of the pelvis, MRI was helpful for staging, concluding that PET/MRI increased diagnostic utility of PET for the management of MIBC [78].

^{18}F- Sodium Fluoride PET/CT and bone scintigraphy

^{18}F-Sodium Fluoride (NaF) is a positron emitting radiopharmaceutical used for PET/CT imaging of bone. ^{18}F-NaF-PET/CT has higher sensitivity and better image quality than bone scintigraphy, making it superior for the detection of osseous metastasis of BCa [79, 80]. Bone scintigraphy is recommended for MIBC patients with suspicious bone metastasis [5]. Preoperative bone imaging is associated with improved survival of MIBC, better patient selection for surgery [81].

Conclusion

Great strides have been made for imaging BCa. Nonetheless, current methods suffer from inaccurate detection of BCa and metastatic lesions. Cystoscopy is recommended for patients with painless hematuria. However, cystoscopy can not accurately show CIS and has difficulty differentiating benign masses from malignant lesions, especially before TURB. Novel cystoscopy techniques are promising for imaging BCa, but further clinical evaluation is needed. US is performed for symptomatic patients to exclude urinary system pathologies. CT is preferred for staging, but cannot differentiate T1 and T2 BCa. MRI can differentiate MIBC from NMIBC and has improved efficacy for local staging. However, MRI is not suitable for patients who have prosthesis or renal failure and is more time consuming than CT. These results are summarized in Table 2. Both CT and MRI have low sensitivity for nodal staging where PET/CT plays a leading role. PET/CT is also important for restaging and assessing treatment response. For PET/CT, ^{11}C-Choline may be an agent of choice since it has low urinary excretion, and higher sensitivity for depicting local relapse. However, the half-life of ^{11}C-choline is short, and requires an in house cyclotron to produce it. These results are summarized in Table 3. ^{18}F-NaF is useful for assessment of blastic bone metastasis. Bone scintigraphy is recommended before TURB. PET/MRI provides better differentiation of normal and pathologic structures as compared with PET/CT. PET/MRI is a relatively novel modality to image BCa. However further studies are needed to evaluate its full potential.

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Glossary of abbreviations

ADC	Apparent Diffusion Coefficient
AUA	American Urological Association
BCa	Bladder Cancer
^{11}C	^{11}Carbon
CEUS	Contrast Enhanced Ultrasonography
CECT	Contrast Enhanced Computed Tomography
CIS	Carcinoma in situ
CLE	Confocal Laser Endomicroscopy
CMP	Corticomedullary phase
CSD	Cumulative incidence of cancer-specific death

CT	Computed Tomography
CTU	Computed Tomographic Urography
2D US	Two-dimensional Ultrasonography
DCE-MRI	Dynamic Contrast Enhanced Magnetic Resonance Imaging
DW-MRI	Diffusion-Weighted Magnetic Resonance Imaging
FC	Flexible Cystoscopy
^{18}F-FDG	^{18}Fluorine-2-deoxy-2-fluorodeoxyglucose
FP	False positive
HTS	Histological T staging
LN	Lymph node
LNMRI	Lymphotropic Nanoparticle Enhanced MRI
mpMRI	Multiparametric MRI
MRI	Magnetic Resonance Imaging
MRU	Magnetic Resonance Urography
nADC	Normalized ADC
NaF	Sodium Fluoride
NBI	Narrow Band Imaging
NCNN	National Comprehensive Cancer Network
NMIBC	Non-Muscle Invasive Bladder Cancer
MIBC	Muscle Invasive Bladder Cancer
NPV	Negative Predictive Value
OCT	Optical Coherence Tomography
OS	Overall survival
RC	Radical Cystectomy
PDD	Photodynamic Diagnosis
PET/CT	Positron Emission Tomography/Computed Tomography
PET/MRI	Positron Emission Tomography/Magnetic Resonance Imaging
PPV	Positive Predictive Value
SPIES	Storz Professional Image Enhancement System

SUV_{max}	Maximum Standardized Uptake Value
1.5T	1.5 Tesla
3T	3 Tesla
TURB	Transurethral Resection of Bladder
T1W-MRI	T1-weighted Magnetic Resonance Imaging
T2W-MRI	T2-weighted Magnetic Resonance Imaging
UTS	Ultrasound T staging
US	Ultrasonography
WLC	White Light Cystoscopy

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Fig. 1.

Sagittal ultrasonography image of the urinary bladder, demonstrating a lobulated mucosal mass with calcifications (*arrow*), representing transitional cell carcinoma of the bladder.

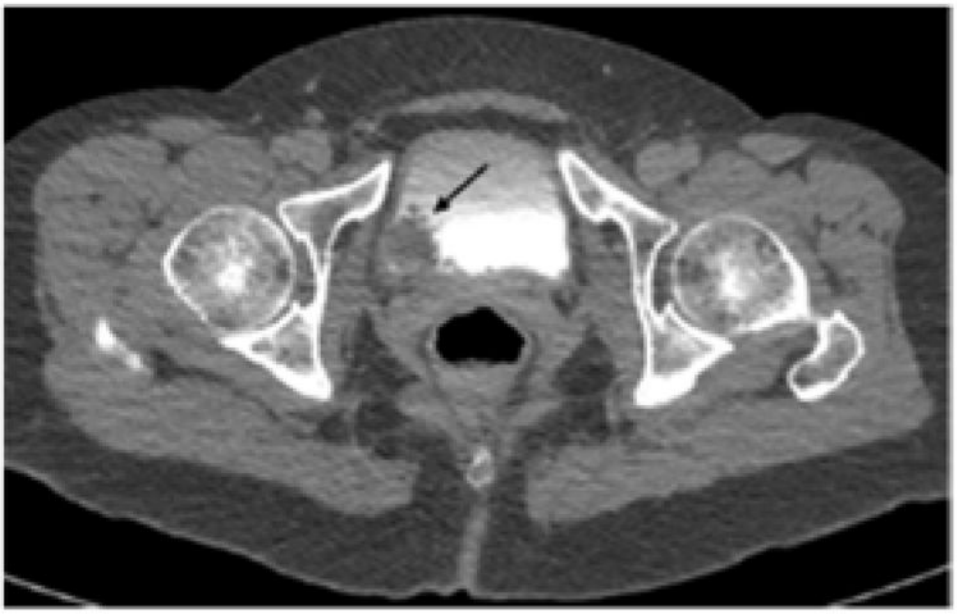

Fig. 2.

Transaxial CT image through the bladder obtained at an 8 minute delay following intravenous contrast administration. The irregular round filling defect in the right posterior aspect of the bladder (*arrow*) represents a transitional cell carcinoma. There is thickening of the adjacent bladder wall, but not definite spread beyond the bladder.

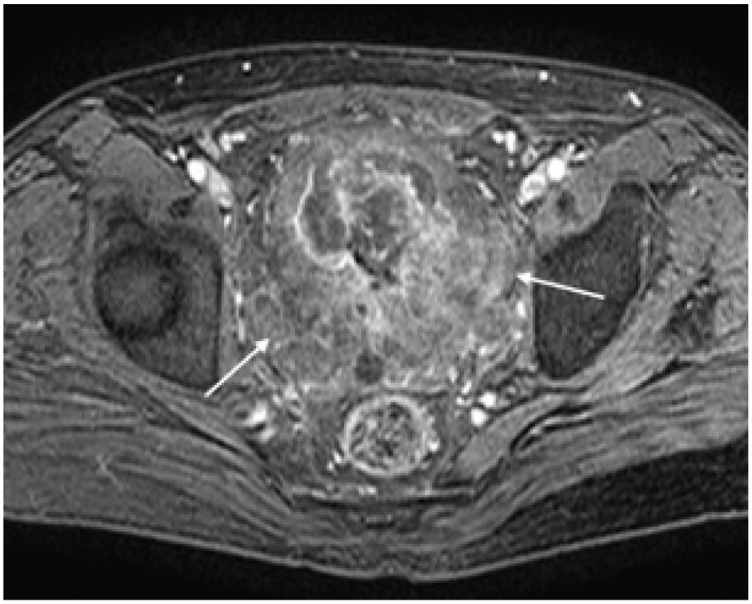

Fig. 3.

Contrast enhanced T1 weighted axial MRI image of the pelvis demonstrates an irregular enhancing mass filling the bladder. The margin of the mass is inseparable from the bladder wall. Irregular enhancement along the bladder wall (*arrow*) suggests transmural spread of disease.

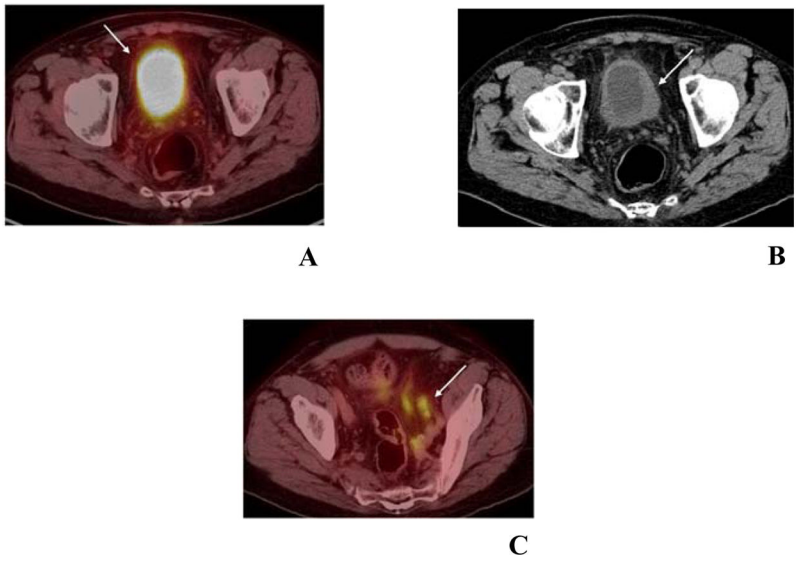

Fig. 4.

78-year-old man with large papillary tumor on left lateral wall and high grade, nonpapillary tumor involving the left trigone just lateral to left UO and posterior left bladder neck on cystourethroscopy.

Due to concentration of ^{18}F-FDG in the urinary bladder, any increased activity of the thickened bladder wall (*arrow*) cannot be determined on the PET/CT image of the pelvis **(A)**. Asymmetric thickening of the left urinary bladder wall (*arrow*), on the pelvis CT part of PET/CT imaging (**B**) and it likely corresponds to known bladder malignancy. Along the left pelvic sidewall there is a 2.4 × 1.3 cm hypermetabolic lymph node with a maximum SUV of 6.17 (**C**).

Table 1

Initial evaluation of suspicious bladder cancer and Recommendations

Modality	Patient condition, status and Recommendations	Reference
Cystoscopy	• microscopic hematuria (in >35 years old): recommended • macroscopic hematuria (all patients): recommended • bladder cancer risk factors (all patients): performed • microscopic hematuria (<35 years old): can be performed according to bladder cancer suspicion	[5,12]
CTU	• Asymptomatic microscopic hematuria: CTU (with and without intravenous contrast agent) is applied with sufficient phases to exclude a renal tumor and an excretory phase to assess upper urinary tract.	[5,12]
MRU	• Recommended for patients with allergies to intravenous contrast agents and renal failure	[5,12]
CT	• Recommended before bladder tumor resection	[5]
MRI	• Recommended before bladder tumor resection • Recommended for patients with allergies to intravenous contrast agents and renal failure	[5,12]
US	• Recommended for patients with allergies to intravenous contrast agents and renal failure	[5,17–21]
PET/CT	• MIBC: staging, follow-up (patients who do not have basal imaging, in high risk patients in case of metastasis suspicion, guidance for biopsy, suspicion of bone metastasis)	[5,6]
Bone scan	• MIBC (suspicion of bone metastasis)	[5]

Note– CT= Computed Tomography, MRI= Magnetic Resonance Imaging, CTU= Computed Tomography Urography, MRU= Magnetic Resonance Urography, US= Ultrasonography, PET/CT= Positron Emission Tomography/Computed Tomography, MIBC= Muscle Invasive Bladder Cancer

Table 2

Accuracy, sensitivity, specificity, PPV for selected modalities for imaging BCa

Modality	n	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	Used for staging	Reference
FC	435	NA	87	10	98	Y	[5, 30]
CTU	687	91.5	86.3	92.4	63.6	Y	[5,27]
CTU	435	NA	87	99	91	Y	[5,30]
CTU	177	92.8	96.3	86.4	92.9	Y	[5,31]
CTU	150	NA	61.5	94.9	53.3	Y	[5,37]
MRU	150	NA	79.9	93.4	52.6	Y	[5,37]

Note– n= Patient number, PPV= Positive Predictive Value, NA= Not applicable, FC= Flexible Cystoscopy, CTU= Computed Tomography Urography, MRU= Magnetic Resonance Urography, Y: Yes

Table 3

Sensitivity, specificity, PPV of selected PET/CT studies for detecting nodal metastases of BCa with recommendations for staging

RF	n	Sensitivity (%)	Specificity (%)	PPV (%)	Used for staging	Reference
^{18}F-FDG	78	56	98	NA	Y	[5,60]
^{18}F-FDG	54	41	86	58	Y	[5,63]
^{18}F-FDG	61	47.1	93.2	72.7	Y	[5,68]
^{18}F-FDG	93	68	95	86	Y	[5,69]
^{11}C-Choline	26	42	84	50	Y	[69,72]
^{11}C-Choline	59	59	90	71	Y	[69,73]

Note– RF= Radiopharmaceutical, n= Patient number, NA= Not applicable, PPV: Positive Predictive Value, ^{18}F-FDG= ^{18}Fluorine-2-deoxy-2-fluorodeoxyglucose, ^{11}C= ^{11}Carbon, Y: Yes